Recent Advances in Pharmacotherapy

Alcohol, barbiturate and benzodiazepine withdrawal syndromes: clinical management

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The symptoms and clinical management of alcohol, barbiturate and benzodiazepine withdrawal syndromes are discussed in this article. People who suffer alcohol withdrawal should be admitted to hospital if they have medical or surgical complications or severe symptoms; supportive care and pharmacotherapy, especially diazepam loading, are the essential components of treatment. Barbiturate withdrawal requires pharmacotherapy and admission to hospital for patients who have taken more than 0.4 g/d of secobarbital or an equivalent amount of another barbiturate for 90 days or longer, or 0.6 g/d or an equivalent dose for 30 days or longer, or who have had withdrawal seizures or delirium; phenobarbital loading is recommended. Regular benzodiazepine therapy that has lasted at least 3 months should be gradually stopped. Short-acting agents should be replaced with long-acting ones, such as diazepam, to avoid withdrawal symptoms. Most of these patients can be managed on an outpatient basis.

Description des manifestations du sevrage de l'alcool, des barbituriques et des benzodiazépines et de leur traitement. Le sujet en voie de sevrage de l'alcool sera hospitalisé si ses symptômes sont graves ou s'il accuse une complication médicale ou chirurgicale; il lui faut surtout un traitement de soutien et une pharmacothérapie, particulièrement sous forme d'une charge de diazépam. Dans le cas du sevrage de barbituriques on hospitalise les malades qui ont pris soit plus de 0,4 g/j de sécobarbital ou une quantité équivalente d'un autre barbiturique depuis au moins 90 jours, soit 0,6 g/j ou l'équivalent pendant au moins 30 jours, et ceux qui présentent des convulsions ou du délire; on recommande alors une charge de phénobarbital. Quant au sevrage des benzodiazépines, si le traitement a duré au moins 3 mois on le cesse graduellement et cherche à éviter les symptômes de manque en remplaçant les dérivés d'action rapide par ceux d'action longue, comme diazépam; la plupart du temps le malade n'a pas besoin d'être hospitalisé.

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The views expressed in this article are those of the author and do not necessarily reflect those of the Addiction Research Foundation.

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Alcohol, barbiturates and benzodiazepines, depressants of the central nervous system (CNS), are subject to abuse and dependence. Acquired tolerance to and physical dependence on these drugs, as with opiates, are manifestations of compensatory neurophysiologic changes that offset the depressant effect on neuronal excitability, impulse conduction and transmitter release. When drug intake is abruptly stopped or decreased the compensatory changes give rise to signs and symptoms of withdrawal, the severity of which varies with the class of drug, the individual and the drug exposure.

Therapy is aimed at relief of symptoms, prevention or treatment of the more serious complications and preparation of the patient for long-term rehabilitation. A rational treatment plan should be

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safe, economical and relatively simple, and its efficacy should be established through methodologically sound studies. Although many of the principles and specifics of treatment have been published,[1-5] much of this information is in specialized journals.

Alcohol withdrawal syndrome

The severity of the alcohol withdrawal syndrome depends on both the intensity and the duration of abuse. Most studies have suggested that the syndrome comprises a continuum of symptoms that range from early mild primary manifestations (e.g., tremulousness) to secondary manifestations or complications (e.g., seizures, hallucinations, arrhythmias and delirium).[6,7] The syndrome can be classified in terms of the timing (early or late), the severity (mild, moderate or severe) and the complications.

The first symptoms to develop are hangover, insomnia and vivid dreams.[8] Anxiety, mild agitation, anorexia, tremor, mild tachycardia (heart rate less than 100 beats/min) and hypertension (blood pressure greater than 150/90 mm Hg) may appear a few hours after the person stops drinking and may disappear within 48 hours. These reactions usually occur after persistent ethanol consumption in excess of 150 to 200 g/d.[7,9] In severe reactions the early symptoms are followed by signs of increasing autonomic activity, disorientation, confusion and auditory or visual hallucinations.[7] Disorientation and global confusion are the diagnostic criteria of delirium tremens.

The risk of illness and death increases if the withdrawal syndrome is not recognized immediately and other illnesses are present.[10] Malnutrition, fever (temperature greater than 40°C), and disturbances in fluid and electrolyte levels are associated with an increased risk of severe withdrawal symptoms.[10] Fewer than 5% of patients in hospital who undergo alcohol withdrawal have a severe reaction;[7] the figure varies considerably depending on the population served by the hospital and on the admission criteria. The mortality rate of a severe reaction is probably less than 2%, because in most centres there is now improved supportive therapy for both the withdrawal syndrome and the concurrent medical complications.

Occasionally patients present with only one prominent clinical manifestation, such as seizure, tremor, hallucinations or cardiac arrhythmia,[1] any one of which should raise the suspicion of alcohol abuse as the primary factor or an associated one.

All patients with late, severe or complicated withdrawal reactions and those with concurrent medical or surgical problems should be admitted to hospital.[1,7] Complete history-taking and physical and laboratory examinations are mandatory because of the multisystem effects of alcohol. Use of the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) scale is a fast, valid and reliable way of quantitating and monitoring key clinical features.[11] The scale is also useful to nursing staff and for educational purposes. (Copies of the scale and instructions for its use are available from the author.)

Supportive care

Uncontrolled studies have shown that reassurance, reality orientation, frequent monitoring of signs and symptoms, and general supportive nursing care can be effective in over two-thirds of the cases of mild alcohol withdrawal syndrome.[12,13] At the Addiction Research Foundation Clinical Institute, Toronto, a standardized supportive care package has been investigated and applied in the treatment of alcohol withdrawal reactions.[11] The procedure includes decreased sensory stimuli, reality orientation, reassurance, maintenance of hydration, nutrition, physical comfort and body temperature, sleep, rest and encouragement toward long-term rehabilitation for 10 minutes every hour while the patient is awake.

In two controlled studies the withdrawal symptoms and signs in 85% of the patients in an emergency department[13] and in 60% of the patients in hospital[14] responded to supportive care within 6 to 8 hours. However, such care does *not* prevent the occurrence of seizures, hallucinations or arrhythmias; hence, pharmacotherapy is usually also indicated.[14]

Pharmacotherapy

The value of multivitamin preparations has not been proven.[1] However, paresis involving the sixth cranial nerve can be reversed with as little as 2 mg of thiamine; typically doses of 25 to 50 mg are given intravenously. Because some patients in severe alcohol withdrawal are malnourished and may have thiamine deficiency without clinical signs, thiamine should be administered to prevent the development of Wernicke's encephalopathy. Prophylactic thiamine therapy should be used in patients who are given glucose intravenously, because the glucose therapy may reveal a relative thiamine deficiency.

The preferred drugs for treatment are the benzodiazepines.[1-5,14,15] The rationale for their use is their cross-tolerance with alcohol.[15] Numerous benzodiazepines, including alprazolam, bromazepam, chlordiazepoxide, clobazam, clorazepate, diazepam, flurazepam, halazepam, lorazepam and oxazepam, have been used. The doses approximately equivalent to 20 mg of diazepam are 100 mg of chlordiazepoxide, 120 mg of oxazepam and 5 mg of lorazepam.[16] Parenteral diazepam therapy is effective in controlling continuous seizure activity.[1] Lorazepam administered sublingually is absorbed rapidly and could be considered for patients with nausea.[13]

Benzodiazepine loading: Benzodiazepines and their metabolites accumulate in the body after repeated daily administration of equal doses of the parent compound.[17] Therefore, desired therapeutic and unwanted toxic effects may not appear before several days of continuous therapy. In the past the consequences of accumulation were avoided by progressive reduction of the dose:[1] doses of diazepam or chlordiazepoxide were decreased at a daily rate of about 25% to 50% of the dose given initially. The effectiveness and simplicity of this approach has been improved.[14] Now a loading dose of diazepam is used because of the long half-lives (greater than 30 hours) of diazepam and *N*-desmethyldiazepam (an active metabolite). Patients in moderate to severe withdrawal are assessed clinically (e.g., with the use of the CIWA-A scale), and 20-mg doses of diazepam are given orally every hour until the patient's condition improves (e.g., to a CIWA-A score of 10 or less) or mild sedation is achieved. There was a faster and greater improvement in patients treated with diazepam loading than in those given placebo;[14] 50% of the patients responded within 7.6 hours to 60 mg of diazepam orally, and most responded within 12 hours. More important, complications occurred exclusively in those treated with placebo; this indicates that a delay in therapy may be responsible for the complications associated with withdrawal. All patients with moderate to severe withdrawal reactions should be given a loading dose of at least 60 mg of diazepam or 300 mg of chlordiazepoxide, and they should be carefully observed. Additional doses are unnecessary if a large enough loading dose has been given, because of the drugs' long half-lives.

Severe agitation, thought disorders, and hallucinations and parahallucinations seem to be controlled with haloperidol (0.5 to 5 mg, intramuscularly or orally); however, research findings are not available to guide optimal therapy. No evidence exists for the need to routinely administer an antiparkinsonian drug. Because haloperidol decreases the seizure threshold patients should also receive chlordiazepoxide or diazepam.[2]

Although diazepam and chlordiazepoxide are most commonly used, clonazepam, flurazepam or other benzodiazepines with long half-lives could presumably be effective.

Treatment of seizures: Seizures are typically major generalized and nonfocal, they occur once or twice, and they most often develop between 6 and 48 hours after drinking has been stopped.[7] Management is required only if the seizures recur or are continuous or life threatening.[1,7]

The therapeutic and prophylactic value of phenytoin is uncertain. In most patients without a history of seizures benzodiazepines alone are probably sufficient to prevent withdrawal seizures.[18-20] Even in those with a history of such seizures, phenytoin appears to offer no advantage over a benzodiazepine, such as diazepam.[21] At the Addiction Research Foundation Clinical Institute diazepam and phenytoin are given only to patients with a prominent history of epilepsy, focal seizures or recurrent multiple withdrawal seizures.

Phenytoin may be effective at serum concentrations of only 12 to 20 μmol/L in cases of alcohol withdrawal, whereas concentrations of 40 to 80 μmol/L are required for optimal control of idiopathic epilepsy.[19] Phenytoin metabolism varies greatly in those with chronic alcoholism;[22] the steady-state blood levels have been found to vary ninefold and to be low in some patients because of increased drug clearance. In the latter patients the estimated mean half-life is only 7.4 (normally 20) hours,[22] and, therefore, to achieve drug concentrations of between 40 and 80 μmol/L the daily maintenance dose may have to be as high as 1000 mg; however, the need for such high doses is rare. Because phenytoin is poorly absorbed if given intramuscularly, oral or intravenous preparations should be used.[20] Plasma concentrations may be measured to ensure optimum management. Therapy should be continued for approximately 5 days, until the risk of seizures has decreased.

Other aspects of management

Adequate identification and early treatment of alcohol withdrawal is only the first step toward full rehabilitation. After the withdrawal reaction subsides patients should enrol in a treatment program for the reduction of alcohol intake and the management of alcohol-related problems.

Barbiturate withdrawal syndrome

Traditionally barbiturates have been classified into categories of long, intermediate, short and ultrashort action, even though the scientific evidence for this classification is not soundly based.[23,24] The barbiturates that produce a withdrawal syndrome (oxybarbiturates) generally have a short to intermediate half-life (10 to 50 hours) and have similar pharmacologic actions; these drugs include pentobarbital, secobarbital, amobarbital and butalbital[25] and are almost by definition being abused, whether obtained legally or illegally, as there are almost no therapeutic indications for long-term treatment. Common at our institution are patients who have abused Fiorinal (butalbital combined with acetylsalicylic acid and caffeine).

Although barbiturate and alcohol withdrawal syndromes share many features, important differences affect management. Barbiturate withdrawal syndrome generally appears somewhat later and is clinically more variable.[26] Severe withdrawal reactions are characterized by seizures and delirium. The convulsions occur between 24 and 115 hours after intake has been stopped.[26] In contrast to alcohol withdrawal, the seizures are more likely to be multiple, two-thirds of the patients having more than one seizure and some having as many as four.

About 60% of the patients subsequently have a psychosis resembling alcohol delirium tremens that lasts from 1 to several days and that is characterized by disorientation as to time and place but not usually person and by hallucinations that are predominantly visual. Deaths have been reported in association with barbiturate withdrawal.[26]

Patients who are chronic abusers of short-acting to medium-acting barbiturates should be assessed to decide whether pharmacotherapy is indicated.[23,25,27] This decision can usually be made on the basis of the following criteria: presence of minor withdrawal symptoms that are severe enough to cause concern; history of daily intake of more than 0.4 g of secobarbital for 90 days or longer (or 0.6 g for 30 days or longer); a documented history of barbiturate or mixed hypnosedative withdrawal seizures or delirium; and the patient's agreement to undergo detoxification in hospital and to discontinue drug use.[27]

Management

Three approaches can be taken to prevent or treat barbiturate withdrawal. The first consists of stabilization with an intermediate-acting barbiturate (e.g., pentobarbital, 0.2 to 0.4 g orally every 4 to 6 hours).[25-27] The second approach involves the use of phenobarbital,[27] which has several advantages over pentobarbital: a slower elimination rate (half-life 86 hours), a large therapeutic window (i.e., a large difference between the toxic and therapeutic doses) and effective anticonvulsant activity.

These two approaches have several disadvantages: uncertainty of dosage, reinforcement of drug-taking behaviour through the repeated administration of barbiturates, difficulties in assessing the clinical state, uncertainty of supplementary doses and drug-seeking by the patient. These issues have been resolved by a third approach, which relies on loading doses of phenobarbital that are titrated to clinical or toxic effects.[23,28] Doses of 120 mg are given every 1 to 2 hours until three of five signs — nystagmus, drowsiness, ataxia, dysarthria and emotional lability — are present or, in symptomatic patients, the withdrawal signs and symptoms disappear. Patients are assessed carefully for evidence of intoxication and of the therapeutic effect of phenobarbital before each subsequent dose is given. In some cases hourly doses are required for 15 to 20 hours, but this is not a problem in hospital. The median loading dose is 1440 mg (mean [and standard deviation] 23.4 [7.1] mg/kg), which results in a median plasma concentration of 150 μmol/L (limits of 57 and 308 μmol/L). With this regimen seizures and delirium do not develop, and withdrawal symptoms are few and minimal. Direct medical supervision is necessary for only 3 days.[28] Discharge or rehabilitation efforts can be considered 2 days after the loading dose has been given. In patients who are acutely ill phenobarbital (0.3 mg/kg per minute) can be infused intravenously.[23]

The phenobarbital dose required for treatment or to reach a safe, mild level of intoxication can indicate the actual extent of drug use, the severity of physical dependence on hypnosedative drugs and the likelihood of a severe withdrawal reaction if the patient is not treated adequately.[23] Those who require less than 7 mg/kg (typically 480 mg) are, in fact, not sufficiently dependent on the drug to require full loading therapy or further treatment.[28]

Phenobarbital kinetics provide the "pharmacokinetic umbrella" to prevent the reappearance of withdrawal symptoms. The half-life is long enough to allow gradual adaptation by the CNS to a drug-free state.[28] The monitoring of phenobarbital concentrations can be used to reassure the patient from the start that the treatment is working well and that the need for additional doses can be determined. However, this practice is usually not necessary.

The loading dose technique has decreased the manipulative drug-seeking behaviour of patients.[28] The systematic titration of the drug dose to specific end-points over a short period has reduced the tendency of the clinician to respond to nonspecific signs to allay the anxieties of the patient and staff members as well as the clinician's anxieties concerning the discomfort of drug withdrawal.

Benzodiazepine withdrawal syndrome

The benzodiazepines have become the preferred drugs in the treatment of anxiety and insomnia, because they are less toxic and have a lower risk of dependence than the barbiturates. Debate continues on the incidence and importance of a withdrawal syndrome after chronic benzodiazepine use is stopped.[29-31] The evidence is now overwhelming that physiologic dependence occurs in cases of high-dosage and low-dosage use.[16,32] The difficulty in diagnosing a withdrawal syndrome has apparently been due to the poor sensitivity of methods to detect withdrawal symptoms and the care and frequency of observation.[16] In addition, the withdrawal symptoms may be mistaken for the pre-existing anxiety, which may recur after treatment is stopped. However, there is a qualitative difference in the nature of the symptoms and in their timing.[16,29-32] Furthermore, the evidence now suggests that long-term therapy (at least 3 months' duration) at normal doses is associated with significant withdrawal symptoms in some patients after the treatment has been stopped and in many after the doses have been decreased too rapidly.[16]

The occurrence and timing of withdrawal symptoms are clearly related to the particular pharmacologic properties of the drug ingested and to the dose and duration of use. The onset of symptoms is directly related to the elimination

rates of the drug and its active metabolites. In general, ultra-short-acting drugs (e.g., triazolam, with a half-life of 2 to 5 hours), short-acting ones (e.g., oxazepam, with a half-life of 6 hours) and intermediate-acting ones (e.g., alprazolam, with a half-life of 12 to 15 hours) may be more likely to produce withdrawal symptoms.[16] Rebound insomnia and rebound daytime anxiety have occurred after as little as 2 weeks of treatment with a short-acting drug.[31] Withdrawal symptoms may occur after 7 days and last as long as 1 month or more if more slowly eliminated drugs such as diazepam have been used. The likelihood of major withdrawal symptoms is reduced with long-acting drugs, although seizures have been reported after high-dose diazepam ingestion had been suddenly stopped.[31,32]

The withdrawal symptoms resemble those associated with high or sometimes therapeutic doses of barbiturates and, to a lesser extent, those associated with alcohol. However, the timing, severity and range of symptoms, which often persist for a long time (up to 8 weeks in some cases) are different, partly because of the prolonged elimination phase of some agents, such as diazepam. Some of the symptoms resemble psychologic manifestations of anxiety, such as tension, difficulty concentrating, fear, fatigue, restlessness and irritability. Others resemble somatic manifestations of anxiety and include headache, insomnia, sweating, tremor, anorexia and dizziness. Some of these symptoms do not represent a return to pre-existing anxiety; anxiety scores (as determined, for example, with the Spielberger Stait-Trait Anxiety Inventory[33]) should not change before, during or after benzodiazepine withdrawal.[16] Other symptoms (muscle ache, flu-like illness and sensory disturbances such as paresthesia, hyperacusis, photophobia and metallic taste) are not typical of anxiety; some of these symptoms, such as sensory disturbances, occur in up to 60% of the patients.[16] It is important to recognize these drug-related symptoms, because they may trigger further drug taking.[16]

Management

The regular benzodiazepine therapy should be ended as soon as possible, preferably within a month. In addition, the dose should be kept as low as possible, because problems are more likely to occur with higher doses, particularly of the shorter-acting agents.[34] Physicians should be careful when prescribing benzodiazepines to patients with a history of drug or alcohol abuse.

A gradual reduction in dosage is appropriate for any patient who has been taking benzodiazepines regularly for more than a few weeks. The regimen will depend on the drug being ingested and its elimination rate; for example, high-dose diazepam therapy (more than 40 mg/d) should be stopped over 8 weeks, but low-dose therapy can be discontinued over 4 to 6 weeks. Short-acting benzodiazepines should be replaced with longer-acting ones, such as diazepam, to avoid withdrawal symptoms that may encourage drug abuse. Dose equivalents can be estimated, and a tapering regimen can be chosen, which will decrease the fluctuation in serum benzodiazepine levels.[16] Doses equivalent to 5 mg of diazepam are approximately as follows: oxazepam 30 mg, chlor-

Table I — Pharmacotherapy for alcohol, barbiturate and benzodiazepine withdrawal syndromes

	Pharmacotherapy			
Syndrome	Drug	Dosage	Duration	Comment
Alcohol withdrawal	Diazepam	20 mg orally every 1 to 2 h	Loading dose: titrate to response;* minimum of three doses	
With hallucinations	Haloperidol	0.5–5.0 mg, orally or intramuscularly		
With seizures	Phenytoin	Loading dose of 10 mg/kg intravenously; maintenance dose of 300–400 mg/d		Use only in patients with history of seizure disorders
Barbiturate withdrawal	Phenobarbital	120 mg (1.7 mg/kg)† orally every 2 h	Loading dose	
Benzodiazepine withdrawal				
Acute	Diazepam	20 mg orally	Load to a total dose of half the daily equivalent of the substance abused	
Chronic	Diazepam	Substitute for average daily dose; gradually stop therapy over 6 to 8 wk		

*A decrease in withdrawal symptoms or the appearance of toxic effects signifies a response.
†Adjust unit dose in patients weighing less than 50 or more than 100 kg.

diazepoxide 25 mg, flurazepam 15 mg, chlorazepate 3.75 mg, bromazepam 3 mg, nitrazepam 2.5 mg, lorazepam 1 mg, triazolam 0.5 mg and alprazolam 0.25 mg.[16]

For patients who have acute withdrawal symptoms diazepam loading (20 mg/h orally) can be used until the symptoms are suppressed.[34] Admission to hospital is advisable. A tapering schedule over 6 to 8 weeks is optimal; however, the dose can be safely decreased by 5% to 10% each day in hospital. The patient may reinstitute drug use after discharge if the symptoms persist. Nonpharmacologic treatments for anxiety, such as cognitive reappraisal and relaxation training, may also be helpful during the gradual reduction of benzodiazepine intake.[16]

Summary

Table I summarizes the pharmacotherapy of alcohol, barbiturate and benzodiazepine withdrawal syndromes. Such therapy must be accompanied by supportive care. Other nonpharmacologic treatments are often important in preventing a return to drug abuse.

I thank Gail Somer for her editorial assistance and Cathy Van Der Giessen for preparing the manuscript.

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